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REVIEW ARTICLE

Strategies to reduce invasive neonatal Group B Streptococcal disease in Malaysia

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Abstract

Invasive neonatal Group B streptococcal (GBS) disease is a globally recognised serious condition. Its most devastating impact is during perinatal and postnatal periods. Epidemiological studies from high-income countries (HICs) showed that maternal rectovaginal GBS colonisation is the leading cause. It was estimated that world-wide, there were 20 million pregnant women with rectovaginal GBS colonisation which has caused 46,200 stillbirths, 40,500 cases of invasive maternal diseases, and 231,800 cases of early-onset and 162,200 cases of late-onset sepsis in neonates/infants. Among neonates/infants who have recovered from the disease, 37,100 suffered neurodevelopmental impairment. The current preventive measures in HICs consist of universal screening for maternal rectovaginal GBS colonisation at 35- to 37-week gestation, followed by intrapartum antibiotic prophylaxis for positive cases. This has prevented more than 80% of early-onset GBS disease. In Malaysian public hospitals, only targeted screening for maternal GBS colonisation was practiced in high-risk women with previous perinatal GBS infection/disease. We do not have national data on a) maternal GBS rectovaginal colonisation rates, b) stillbirths caused by GBS infections, c) preterm birth associated with maternal GBS colonisation, and d) neurodevelopmental impairment following invasive neonatal GBS disease. We only have national data of neonatal GBS sepsis which showed high morbidity and mortality. To reduce invasive neonatal GBS disease in Malaysia, we need national data on the prevalence of maternal GBS rectovaginal colonisation, its associated risk with stillbirths, and GBS-associated preterm births to help improve current preventive strategies to reduce invasive GBS disease during the perinatal and postnatal periods.

Keywords: group B *Streptococcus*, neonatal sepsis, stillbirths, preterm birth, Malaysia

INTRODUCTION

Invasive *Streptococcus agalactiae* or Group B streptococcal (GBS) disease is a globally recognised serious condition, affecting pregnant women, their foetuses, neonates, young infants, immunocompromised adults, and the elderly. Its most devastating impact is during the perinatal period.[1] Maternal rectovaginal GBS colonisation is a leading cause of invasive disease in pregnant women[2], their foetuses and neonates in many countries.[3,4,5] Ascending spread of maternal rectovaginal GBS colonisation causes intra-amniotic infections, early postpartum bacteraemia, endometritis, maternal urinary tract infections, foetal infections, third-trimester stillbirths, and premature deliveries.[6] During birth, exposure to maternal rectovaginal colonisation leads to invasive early-onset (day 0-6 of life) and late-onset (day 7-89 of life) neonatal/infant GBS disease (such as sepsis, pneumonia, meningitis), and high mortality. Furthermore, survivors of neonatal GBS sepsis with or without meningitis were reported to have increased risk of neurodevelopment impairment (NDI) needing special education.[7]

BURDEN OF INVASIVE GBS DISEASE WORLD-WIDE

The estimated global incidence of invasive GBS disease in recent years was 0.49 (95% CI: 0.43-0.56) per 1000 livebirths.[8] Most epidemiological studies of maternal GBS colonisation and burden

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of GBS disease were conducted in high-income countries (HICs).[1] Paul P *et al*.[9] estimated that world-wide there were 20 million pregnant women with rectovaginal GBS colonisation which had caused 46,200 stillbirths, 40,500 cases of invasive maternal diseases, and 231,800 cases of early-onset and 162,200 cases of late-onset diseases in infants. Among infants who recovered, 37,100 had moderate or severe neurodevelopmental impairment. Seale *et al*.[10] estimated that globally, early-onset GBS disease was more common than late-onset disease, and Asia had the highest number of early-onset disease while Africa had the highest number of late-onset GBS disease. Furthermore, GBS remains the leading cause of meningitis during the neonatal period.[11]

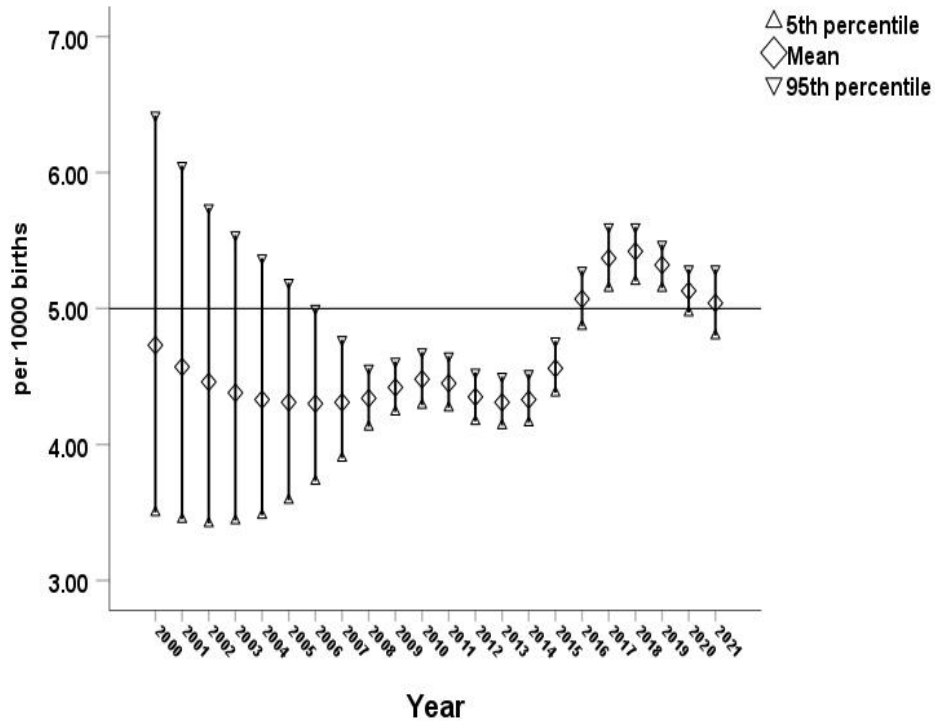
BURDEN OF GBS DISEASE IN MALAYSIA

Like many LMICs, Malaysia does not have national data on the rates of a) maternal GBS rectovaginal colonisation, b) stillbirths caused by GBS infections, c) preterm birth associated with maternal GBS colonisation, and d) neurodevelopmental impairment following invasive neonatal GBS disease. The only national GBS data we have are those of neonatal GBS sepsis, both early-onset sepsis (EOS, ≤72 hours of life)[12], and late-onset sepsis (LOS, >72 hours of life).[13] Based on a six-year (2015-2020) study using data from 44 neonatal intensive care units (NICUs) participating in the Malaysian National Neonatal Registry (MNNR), the incidence of EOS GBS sepsis among inborn neonates was 0.20/1000 livebirths, and LOS GBS sepsis was 0.03 per 1000 livebirths.[12,13] Theses incidences were probably under-estimated as the out-born neonates were not included in the calculation. Nevertheless, all the major public hospital NICUs contributed data to the MNNR which revealed that GBS was the most common cause of neonatal EOS in Malaysian NICUs.[12] GBS accounted for 39.2% of the pathogens isolated from neonates with EOS. The incidence of GBS EOS increased from 0.17 per 1000 livebirths in year 2015 to 0.22 per 1000 livebirths in year 2020. GBS EOS occurred most frequently in term-gestation neonates. GBS was the most common cause of EOS in very low birthweight (VLBW, <1500 g) neonates. In VLBW neonates with GBS EOS, the majority (93.4%) were very preterm (<32-week gestation) neonates. Mothers of neonates with GBS EOS were younger, and higher proportions of them were primigravida, Malays, and/or had chorioamnionitis than mothers of neonates without EOS. The mortality rate of GBS EOS was high (21.4%). In neonates with LOS[13], GBS was the most common gram-positive pathogen (48.1%) isolated in term-gestation neonates and had the highest mortality rate (26%) among all neonates with gram-positive LOS. Meningitis was more common in neonates with GBS LOS than GBS EOS and was associated with high morbidity and mortality like those reported in other countries.[14,15]

Studies in HICs showed that the national incidence of neonatal GBS EOS reflects the prevalence of maternal GBS colonisation in a country and the risk of perinatal diseases. In Malaysia, the stillbirth rates remained static for over 21 years, and in the recent seven years (2015-2021), there was a gradual upward trend (Fig. 1).[16] This rising trend parallels the rising trend of GBS EOS rates in Malaysian NICUs during the same period of time.[12] Without national data on the rates of maternal GBS colonisation and GBS-associated stillbirths, it is impossible to determine whether GBS infection could be an important modifiable factor for reducing stillbirth, prematurity and neonatal GBS sepsis rates in Malaysia.

CURRENT GBS PREVENTIVE MEASURES IN OTHER COUNTRIES

The current preventive measures against perinatal GBS in many HICs consist of universal screening for maternal rectovaginal GBS colonisation at 35- to 37-week gestation, followed by intrapartum antibiotic prophylaxis (IAP) for positive cases.[17] This practice has prevented more than 80% of early-onset GBS disease in many HICs.[18] However, even in these countries, owing to incomplete coverage of susceptible pregnant women, some cases of early-onset GBS disease still occur. Furthermore, these measures did not prevent stillbirths, GBS-associated preterm births, and late-onset GBS disease after 7 days of life[19,20], which were showing an increasing trend in recent years in these countries.[14,21] Given the high public health burden of GBS world-wide and the logistic problems associated with universal screening and IAP in resource-limited LMICs, the World Health Organisation (WHO) Product Development for Vaccine Advisory Committee has identified GBS as a high priority for the development of a vaccine for maternal immunisation.[22] Recent clinical trials of maternal GBS vaccination suggest its potential to provide protection against GBS disease by reducing maternal infections, stillbirths, GBS-associated



Data source from World Health Organisation.[16]

Figure 1. Stillbirth rates in Malaysia, 2000-2021.

preterm births, early-onset GBS and late-onset GBS diseases, and long-term NDI.[23,24]

CURRENT GBS PREVENTIVE MEASURES IN MALAYSIA

In Malaysia, universal screening for maternal GBS colonisation is not the standard of care in public hospitals. According to our national guidelines published by the Ministry of Health[25], the current national policy to reduce neonatal invasive GBS disease is to use targeted screening for maternal colonisation in high-risk pregnant women who had a history of "previous baby with invasive GBS disease, preterm labour, GBS carriage in previous pregnancy, prolonged premature rupture of membrane in known GBS carrier, GBS carriage in current pregnancy and for maternal chorioamnionitis". This policy excluded most of the first-time mothers. Yet a recent multicentre study over a six-year period[12] showed that young mothers and primigravida were statistically significant factors associated with increased risk of neonatal GBS EOS in Malaysian NICUs. This, to some extent, explained why targeted screening was not effective in reducing the burden of invasive neonatal GBS disease in Malaysia.

PROPOSED STRATEGIES TO REDUCE INVASIVE NEONATAL GBS DISEASE IN MALAYSIA

Studies on universal screening and IAP practice in HICs, and recent trials on maternal GBS vaccination show that invasive GBS disease is preventable and can be mitigated. To reduce invasive neonatal GBS disease in Malaysia, we need to replace the practice of targeted screening for GBS by universal screening practice. We also need to systematically collect the results of the screening test to provide information on the prevalence of maternal GBS rectovaginal colonisation, and its associated risk with stillbirths, GBS-associated preterm births, and all neonatal and early infancy GBS diseases. Currently, the neonatal GBS disease data were only from the 44 Malaysian NICUs participating in the MNNR. We also need data on the long-term neurodevelopmental outcome of survivors of neonatal GBS disease to assess its impact on the socio-economic burden in our society.

Furthermore, instead of using only traditional microbiological culture methods, we should consider using molecular methods such as targeted polymerase chain reaction (PCR) tests[26] for the screening of maternal GBS colonisation, GBS-associated stillbirths and preterm labour, and for the investigation of neonates suspected to have GBS sepsis. These methods would provide rapid and more accurate information on the burden of GBS infection in Malaysia. The continuing collection of these screening data nation-wide will also help us to monitor the impact of the screening program, IAP practices, cost-effectiveness, and future vaccination programs on maternal colonisation rates, stillbirth rates, GBS-associated preterm rates, neonatal GBS EOS and LOS, neonatal mortality rates and their long-term neurodevelopmental outcome in survivors and their emotional, societal, and economic impact in our country.

Conflicts of interest: I do not have any conflict of interest that could potentially be construed to affect the material contained in this manuscript that is being submitted to the Journal.

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